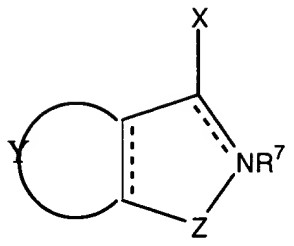


I

and having an IC_{50} of 100 μM or lower for inhibiting poly(ADP-ribose) polymerase *in vitro*,

or a pharmaceutically acceptable base or acid addition salt, prodrug, metabolite, optical isomer or stereoisomer thereof, wherein:

X is double-bonded oxygen or -OH;

R^7, when present, is hydrogen;

Y represents the atoms necessary to form a fused phenyl, pyridine, or pyrimidine ring; and

Z is $-R^6C=CR^3-$ wherein R^6 and R^3, taken together, form a fused phenyl, pyridine, or pyrimidine ring;

wherein said fused phenyl, pyridine, or pyrimidine ring of Y or Z is independently unsubstituted or substituted with at least one non-hydrogen, non-interfering substituent.

REMARKS

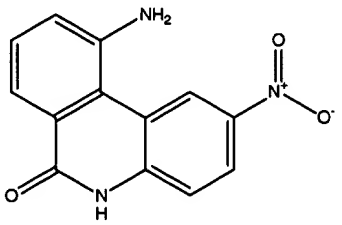
Reconsideration is requested.

Claims 184-233 are pending. Claims 217, 224, 227 and 229 have been amended above to obviate the potential Rule 75 objection to claims 217, 224, 227, 229, 220, 225, 228 and 230. Support for the amendments may be found throughout the

specification and the originally filed claims, such as, for example, claim 145, which supports the amendment to claim 217; claim 150, which supports the amendment to claim 224; claim 152, which supports the amendment to claim 227; and claim 153, which supports the amendment to claim 229. The pending claims are defined by the elected Group II, which the Examiner defined as original claims 99-155. No new matter has been added. The claims have been amended to advance prosecution by obviating the potential Rule 75 objection to the above noted claims. Entry of the above and withdrawal of the Examiner's potential objections in paragraphs 2 and 3 of the Office Action dated October 30, 2000 (Paper No. 16) are requested.

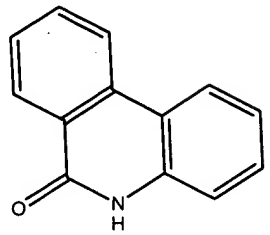
The applicants note a species election was made in the Response of March 15, 2000, to the compound of claim 125 with a mode of delivery of sterile solution, preferably for intravenous administration, and an indication of treating ischemia/reperfusion. The Examiner has withdrawn claims 193-195, 197-206, 208, 214, 215, 218-291, 221-223, 226 and 231-233 from consideration as being drawn to a non-elected species where there is allegedly no allowable generic or linking claim. Upon entry of the above, claims 217, 220, 224, 225, 227, 228, 229 and 230 should also be withdrawn from further consideration if no allowable generic or linking claim is identified.

The Examiner will appreciate that the elected species has the following structure:



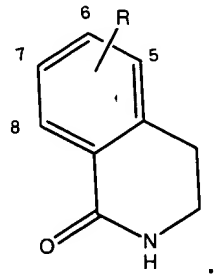
5(H)2-nitro-10-aminophenanthridin-6-one.

Moreover, 6(5H)-phenanthridinone, as described in Weltin (Onocology Research 6:399-403 (1994)) has the following structure:



6(5H)-phenanthridinone

Finally, Suto (Anti-Cancer Drug Design, Vol. 7, 107-117 (1991)) discloses dihydroisoquinolinones of the following structure:



The Section 103 rejection of claims 184-192, 196, 207, 209-213, 216-217, 220, 224, 225, and 227-230 over Weltin in view of Suto and Endres (Journal of Cerebral Blood Flow and Metabolism, 17 (11) 1143-1151 (1991)) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

The Examiner's combination of references would, at best, only provides an invitation to further experimentation rather than making the presently claimed invention

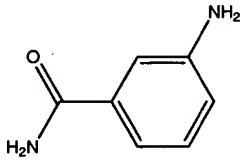
obvious. Specifically, Suto relates to isoquinolinones and dihydroisoquinolinones, as opposed to phenanthridinones of Weltin and the presently elected invention.

The Examiner has asserted that phenanthridinones of Weltin, for example, "are generally considered as derivatives of isoqinolinones [sic]. See, the Abstract of Weltin et al." See, page 3 of Paper No. 16. The Examiner has not indicated however nor does the art describe that substitutions made to a dihydroisoquinolinone or an isoquinolinone would have the same biological outcome or effect as substitutions made to a phenanthridinone, such as described by Weltin. Accordingly, even if Weltin describes that his phenanthridinone is an isoquinolinone derivative, the Examiner has failed to address the applicants' previous comments with regard to the reported loss of activity which was described in Suto when substituting the dihydroisoquinolinones of Suto from the 5 position to the 6, 7, or 8 positions, as described on page 116 of Suto. Clearly, it would not have been obvious what the activity of the resulting compound would be if one were to fuse a six-membered ring to the dihydroisoquinolinone of Suto to produce a phenanthridinone, such as described in Weltin, and then make substitutions, such as are described in Suto, and then further substitute the additionally fused ring, to make the elected species.

Moreover, there is no motivation in the cited art to make such a modification of Suto as one would be required to not only substitute Suto's dihydroisoquinolinone but also substitute in the additional fused ring to form the elected species. The Examiner's reference to motivation being found in a desire to "modify or optimize the structure of 6(5H)- phenanthridinone for similar or better activity" (see, page 3 of Paper No. 16) is,

with all due respect, submitted to only be an invitation to experiment as opposed to the motivation required to establish a *prima facie* case of obviousness.

The cited Endres reference relates to the use of 3-aminobenzamide, which has the following structure:



3-aminobenzamide

which is further from the phenanthridinones of Weltin than the isoquinolinones and dihydroisoquinolinones of Suto. Accordingly, it is unclear what aspect of Endres would have been used to motivate one of ordinary skill in the art to make the presently claimed invention. Clarification is requested in this regard in the event the rejection is maintained.

The Examiner indicates in Paper No. 16 that Weltin describes 6(5H)-phenanthridinone as blocking PARP activity at "micromolar concentration". While this may be true, the applicants respectfully submit that the presently claimed invention is not directed to the phenanthridinone of Weltin and, moreover, Suto has demonstrated that variable substitutions around a ring structure, such as dihydroisoquinolinones, can result in a "loss of activity". Accordingly, it would not have been obvious that PARP inhibition activity would have been maintained by substitution of Weltin's compound.

Withdrawal of the Section 103 rejection is requested along with examination of further species within the elected Group.

In view of the above, the claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

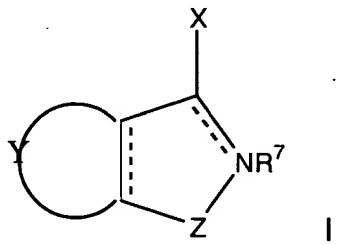
By: _____

B. J. Sadoff
Reg. No. **36,663**

BJS:eaw
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

MARKED-UP CLAIMS

217. (Amended) A method of [effecting a neuronal activity] treating inflammation in a mammal comprising administering to said mammal an effective amount of a compound of formula I containing at least one ring nitrogen:



I

and having an IC_{50} of 100 μM or lower for inhibiting poly(ADP-ribose) polymerase *in vitro*,

or a pharmaceutically acceptable base or acid addition salt, prodrug, metabolite, optical isomer or stereoisomer thereof, wherein:

X is double-bonded oxygen or -OH;

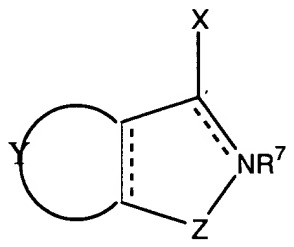
R^7, when present, is hydrogen;

Y represents the atoms necessary to form a fused phenyl, pyridine, or pyrimidine ring; and

Z is $-R^6C=CR^3-$ wherein R^6 and R^3, taken together, form a fused phenyl, pyridine, or pyrimidine ring;

wherein said fused phenyl, pyridine, or pyrimidine ring of Y or Z is independently unsubstituted or substituted with at least one non-hydrogen, non-interfering substituent.

224. (Amended) A method of <u>treating septic shock</u> [effecting a neuronal activity] in a mammal comprising administering to said mammal an effective amount of a compound of formula I containing at least one ring nitrogen:



I

and having an IC_{50} of 100 μM or lower for inhibiting poly(ADP-ribose) polymerase *in vitro*,

or a pharmaceutically acceptable base or acid addition salt, prodrug, metabolite, optical isomer or stereoisomer thereof, wherein:

X is double-bonded oxygen or -OH;

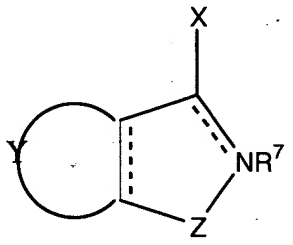
R^7, when present, is hydrogen;

Y represents the atoms necessary to form a fused phenyl, pyridine, or pyrimidine ring; and

Z is $-R^6C=CR^3-$ wherein R^6 and R^3, taken together, form a fused phenyl, pyridine, or pyrimidine ring;

wherein said fused phenyl, pyridine, or pyrimidine ring of Y or Z is independently unsubstituted or substituted with at least one non-hydrogen, non-interfering substituent.

227. (Amended) A method of [effecting a neuronal activity] <u>treating diabetes</u> in a mammal comprising administering to said mammal an effective amount of a compound of formula I containing at least one ring nitrogen:



I

and having an IC_{50} of 100 μM or lower for inhibiting poly(ADP-ribose) polymerase *in vitro*,

or a pharmaceutically acceptable base or acid addition salt, prodrug, metabolite, optical isomer or stereoisomer thereof, wherein:

X is double-bonded oxygen or -OH;

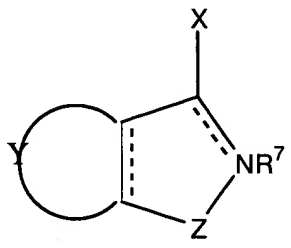
R^7, when present, is hydrogen;

Y represents the atoms necessary to form a fused phenyl, pyridine, or pyrimidine ring; and

Z is $-R^6C{=}CR^3-$ wherein R^6 and R^3, taken together, form a fused phenyl, pyridine, or pyrimidine ring;

wherein said fused phenyl, pyridine, or pyrimidine ring of Y or Z is independently unsubstituted or substituted with at least one non-hydrogen, non-interfering substituent.

229. (Amended) A method of [effecting a neuronal activity] <u>treating arthritis</u> in a mammal comprising administering to said mammal an effective amount of a compound of formula I containing at least one ring nitrogen:



I

and having an IC_{50} of 100 μM or lower for inhibiting poly(ADP-ribose) polymerase *in vitro*,

or a pharmaceutically acceptable base or acid addition salt, prodrug, metabolite, optical isomer or stereoisomer thereof, wherein:

X is double-bonded oxygen or -OH;

R^7, when present, is hydrogen;

Y represents the atoms necessary to form a fused phenyl, pyridine, or pyrimidine ring; and

Z is $-R^6C=CR^3-$ wherein R^6 and R^3, taken together, form a fused phenyl, pyridine, or pyrimidine ring;

wherein said fused phenyl, pyridine, or pyrimidine ring of Y or Z is independently unsubstituted or substituted with at least one non-hydrogen, non-interfering substituent.